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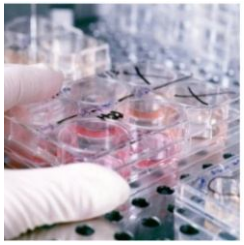

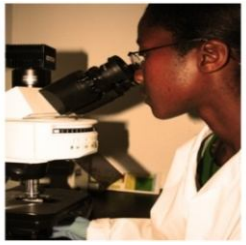

What is new about diagnosis (and treatment) of viral infections

Marvin Hsiao

SAPA ID workshop

September 2014

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Key messages:

Advances in molecular diagnostics in terms of :

- Simultaneous detection of multiple pathogen
- Point-of-Care

Not much in new antivirals

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Traditional viral diagnostics

- Long turn-around time
- Retrospective
- “Catch-all”
- “Cheap”
- Subjective
- Qualitative
- Labour intensive
- Phenotypic

Molecular diagnostics

- Short turn-around time
- Influence pt management
- Virus specific
- Expensive
- Objective
- Quantitative
- Automated
- Genotypic

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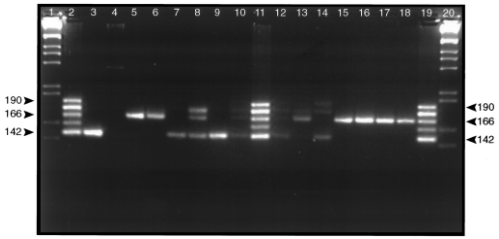
1980 1990 2000 2010

ELISA PCR Quantitative PCR ?



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Example diagnosis of CMV

1980 1990 2000 2010

	CMV IgM	CMV pp65 antigenaemia	CMV PCR	CMV VL	Ganciclovir resistance genotyping
Sensitivity	poor	average	good	good	
Specificity	poor	poor	poor	good	
Labour	3 hours	4 hours	3 hours	2 hours	8 hours+
Turnaround	5 days	Same day	3 days	Same day	2 weeks
Cost*	R110	R300	R375	R375	Priceless ?

* Approximate NHLS prices for the state sector 2014

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Traditional viral diagnostics

- Long turn-around time
- Retrospective
- "Catch-all"
- Cheap
- Subjective
- Qualitative
- Labour intensive
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Modern viral diagnostics

- Short turn-around time
- Influence pt management
- Virus specific
- Expensive
- Objective
- Quantitative
- Automated
- Genotypic

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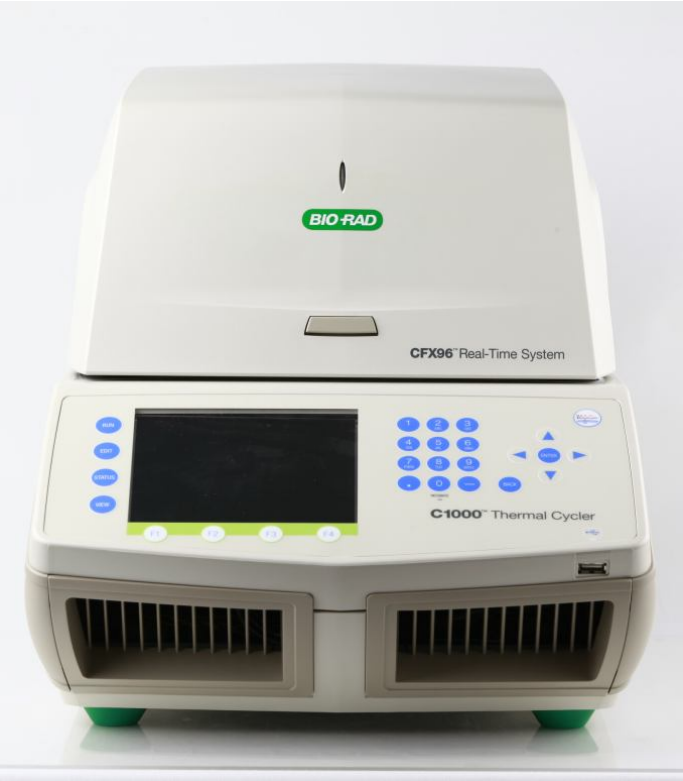
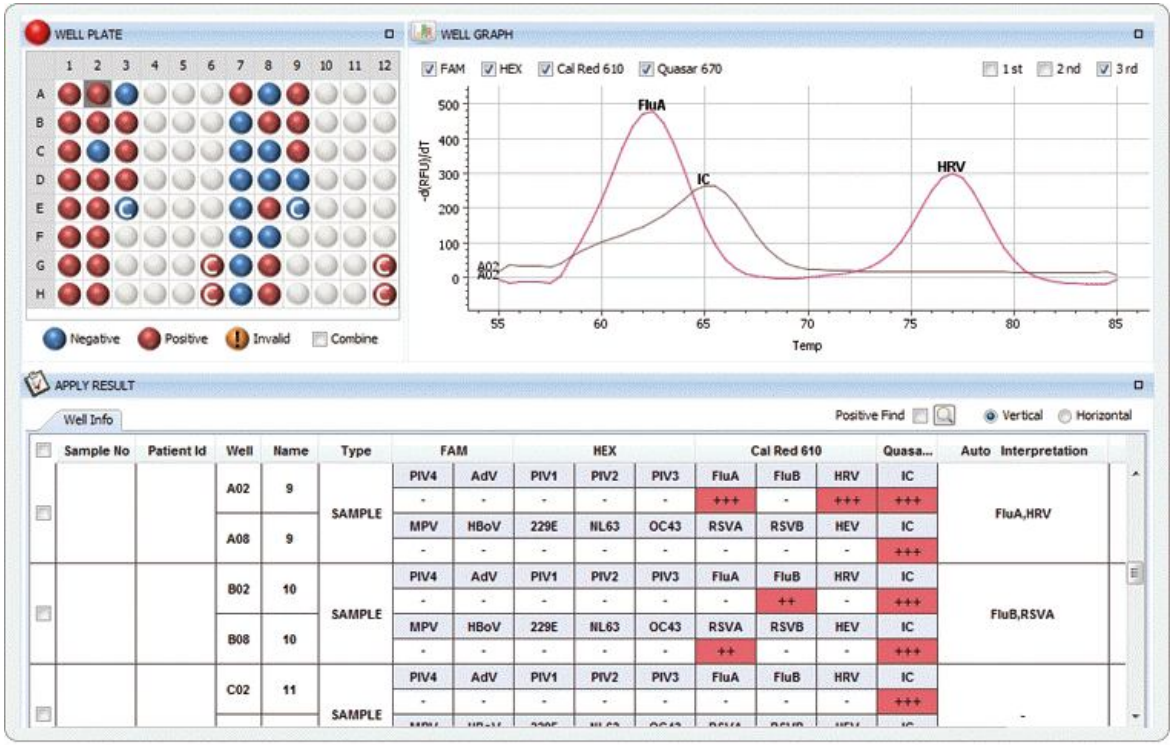
Seegene

Anyplex RV 16 Panel A	Anyplex RV 16 Panel B
- Adenovirus (AdV)	- Respiratory syncytial virus A (RSV A)
- Influenza A virus (FluA)	- Respiratory syncytial virus B (RSV B)
- Influenza B virus (FluB)	- Bocavirus 1/2/3/4 (HBoV)
- Parainfluenza virus1 (PIV1)	- Metapneumovirus (MPV)
- Parainfluenza virus2 (PIV2)	- Coronavirus 229E (CoV 229E)
- Parainfluenza virus3 (PIV3)	- Coronavirus NL63 (CoV NL63)
- Parainfluenza virus4 (PIV4)	- Coronavirus OC43 (CoV OC43)
- Rhinovirus A/B/C (HRV)	- Enterovirus (HEV)





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fast-track DIAGNOSTICS

FTD Meningitis multiplex PCR

- Herpes simplex virus 1, 2
- Varicella-zoster virus
- Enterovirus
- Mumps virus
- Parechovirus

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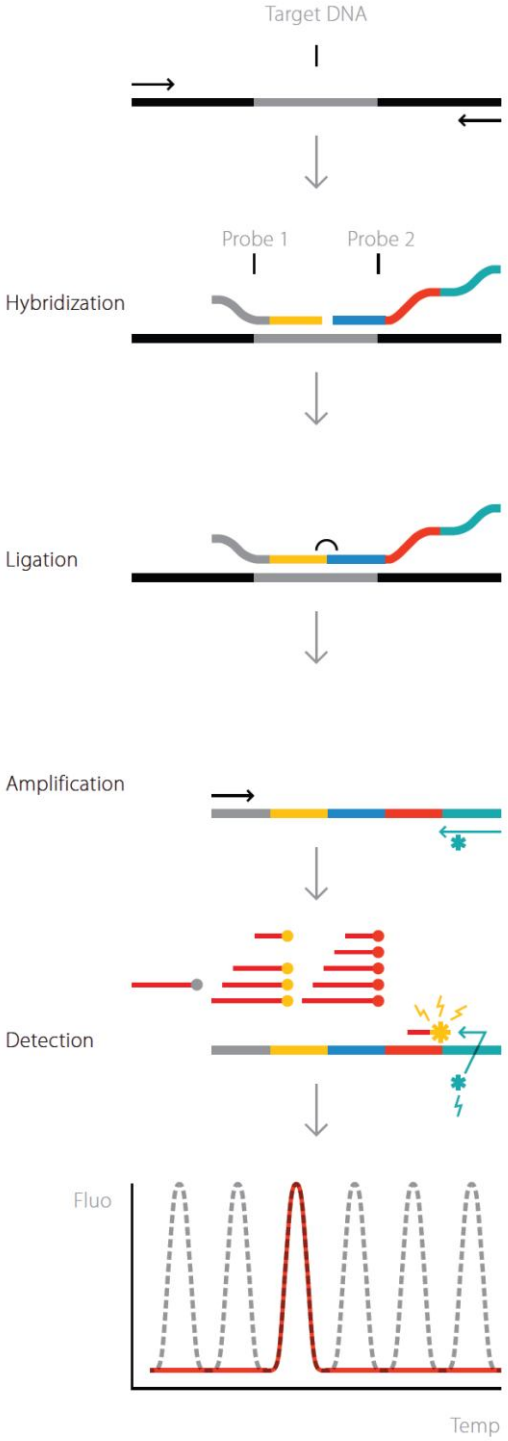
PathoFinder®

Targets

Bacteria
Campylobacter jejuni
Campylobacter spp.
Clostridium difficile toxin A/B
Escherichia coli O157:H7
Salmonella spp.
Shiga toxin-producing E. coli (STEC)
Shigella spp.
Yersinia enterocolitica
Aeromonas spp.
Parasites
Giardia lamblia
Entamoeba histolytica
Cryptosporidium spp.
Dientamoeba fragilis
Viruses
Adenovirus (F40/41)
Astrovirus
Rotavirus (A)
Norovirus (GI/GII/GIV)



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Limitations

- "Dead" nucleic acid vs live organism?
  - Implications in risk of nosocomial spread
- Panel of pathogens offered by commercial kits
  - Too many, not enough, not relevant
  - Clinical significance of pathogen to be established
- How to interpret the result in case of
  - URT "normal flora"
  - Weak positive signal
- Cost

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POC viral load & EID products: available and pipeline*

SAMBA I VL
DDU/Cambridge

SAMBA EID
DDU/Cambridge

Alere q
Alere

ZIVA™
Cavidi

EOSCAPE HIV™
Wave 80 Biosciences

RT CPA HIV-1 Viral Load
Ustar

GeneXpert
Cepheid

Liat™ Analyser
IQuum

Savanna Viral Load Platform
NWGHF

Gene-RADAR
Nanobiosm

Micronics

LYNX HIV p24 Antigen
NWGHF

Truelab PCR
Molbio/bigTec

Viral Load Assay with BART Lumora

2013 2014 2015 2016

*Estimated as of May 2014 - timeline and sequence may change.

----No market launch date set by company.

Built in Battery

The assay continues to run even if there is unexpected cut to the power supply

User Interface

Touch Screen

Data storage of

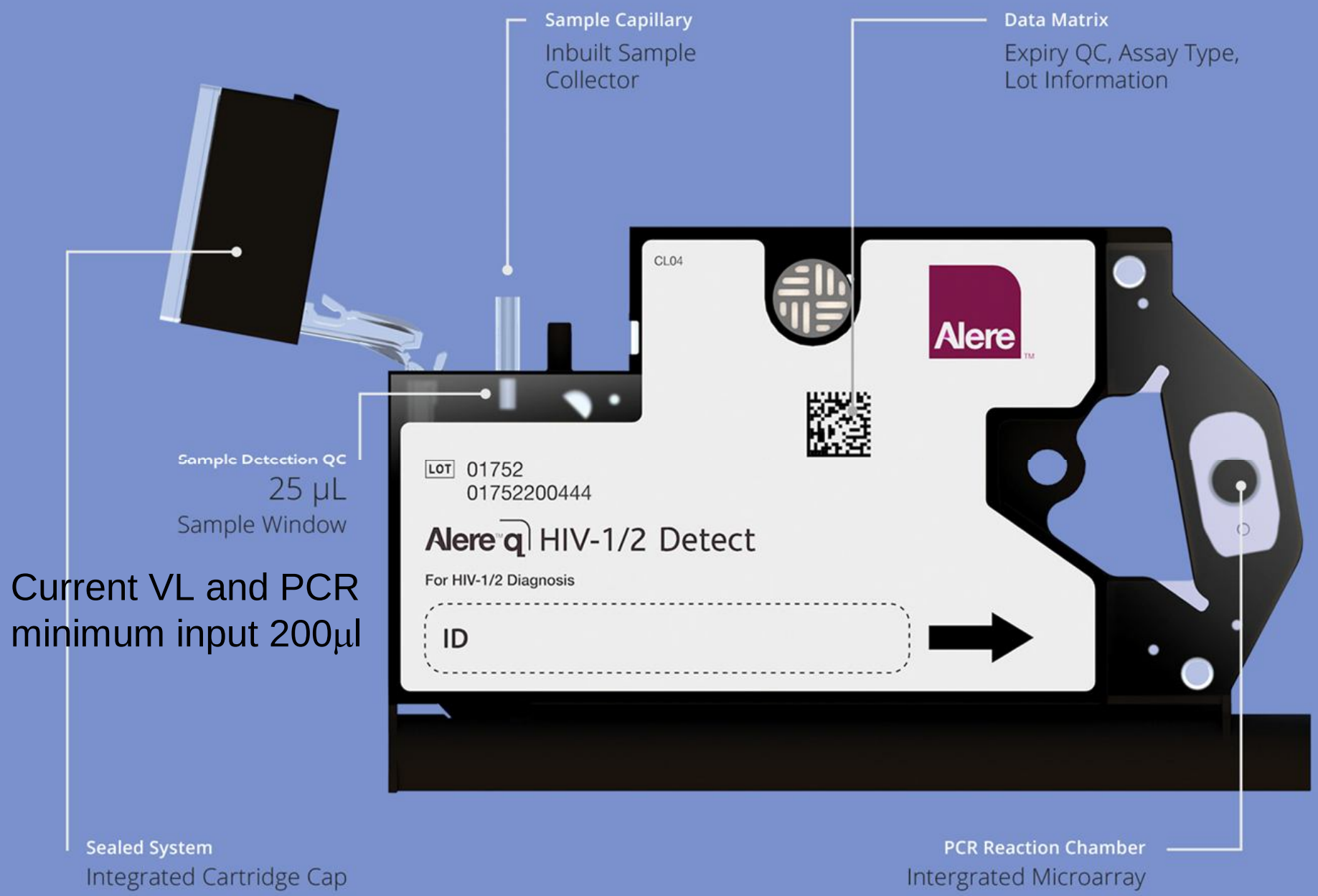
1000 Tests

Automated Testing

Simple Procedure, Built in Controls

Dimensions:
D 31 cm x W 20 cm x H 22 cm

7.8 kg


Sample Capillary
Inbuilt Sample Collector
Data Matrix
Expiry QC, Assay Type, Lot Information
CL04
Alere
Sample Detection QC
25 µL
Sample Window
LOT 01752
01752200444
Alere q HIV-1/2 Detect
For HIV-1/2 Diagnosis
ID
Current VL and PCR minimum input 200µl
Sealed System
Integrated Cartridge Cap
PCR Reaction Chamber
Intergrated Microarray

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Evaluation of Alere q as early infant diagnosis tool

	Alere q point-of-care HIV PCR			
	Error	Negative	Positive	Total
Roche CAP/CTM HIV-1 PCR				
Negative	55	828	2	885
Positive	10	5	146	161
Equivocal	0	5	6	11
Total	65	838	154	1057

- 6% error rate; 66% of the errors resolved on the 2nd attempt; error more common among newborns
- Sensitivity 96.7% Specificity 99.4%
- Excluding error 99.3% concordance; including error 93.1% concordance

Hsiao et al. Unpublished data

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Evaluation of Alere q as whole blood VL quantification

Khan et al. Unpublished data

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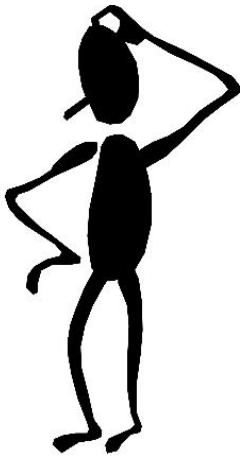
Limitations



- Error/maintenance
- Throughput
- Place
- Cost
- Quality

- New model of diagnostic service require partnership between clinicians, labs and industry

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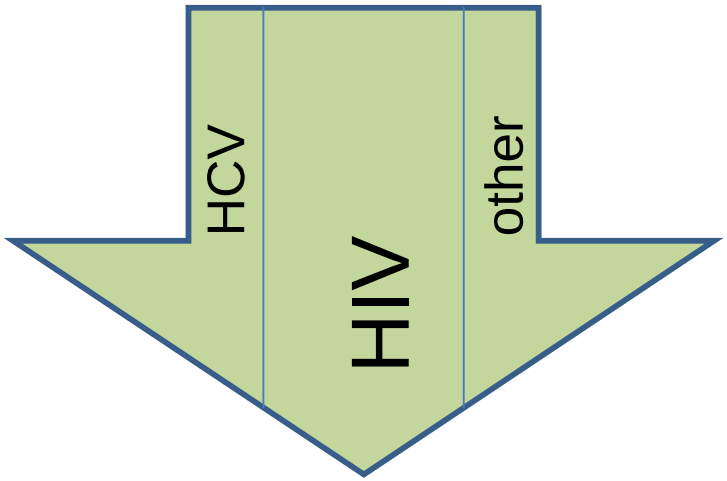
Antiviral research & development



Phase 1 clinical trial in adult

Phase 2+3 clinical trial in adult

Phase 2+3 clinical trial in children

Licensed in South Africa

Difficulty:

- Small market
- Design appropriate clinical trial
- Few chronic viral diseases in children

Evidence:

- Use in life threatening viral infection

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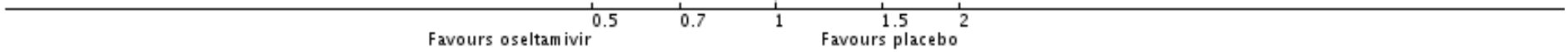
Jefferson et al. Cochrane Database Syst Rev April 2014

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children
Comparison: 1 Oseltamivir versus placebo for treatment
Outcome: 48 Defined as influenza-infected at baseline in child treatment

Study or subgroup	Oseltamivir n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
NV16871	43/165	51/164		7.3 %	0.84 [0.59, 1.18]
WV15758	216/342	235/353		71.4 %	0.95 [0.85, 1.06]
WV15759/WV15871	84/170	95/165		21.3 %	0.86 [0.70, 1.05]
Total (95% CI)	**677**	**682**		**100.0 %**	**0.92 [0.84, 1.01]**

Total events: 343 (Oseltamivir), 381 (Placebo)
Heterogeneity: Tau² = 0.0; Chi² = 1.05, df = 2 (P = 0.59); I² =0.0%
Test for overall effect: Z = 1.76 (P = 0.079)
Test for subgroup differences: Not applicable

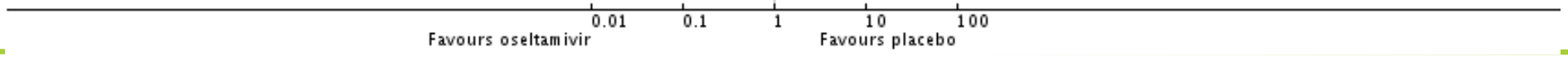


Duration of symptom decrease 29 hrs

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children
Comparison: 1 Oseltamivir versus placebo for treatment
Outcome: 52 Complications: pneumonia in child treatment

Study or subgroup	Oseltamivir n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
NV16871	3/165	6/164		15.9 %	0.50 [0.13, 1.95]
WV15758	16/342	13/353		58.0 %	1.27 [0.62, 2.60]
WV15759/WV15871	7/170	6/165		26.1 %	1.13 [0.39, 3.30]
Total (95% CI)	**677**	**682**		**100.0 %**	**1.06 [0.62, 1.83]**

Total events: 26 (Oseltamivir), 25 (Placebo)
Heterogeneity: Tau² = 0.0; Chi² = 1.44, df = 2 (P = 0.49); I² =0.0%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Prichard & Kern, Virus research 2011

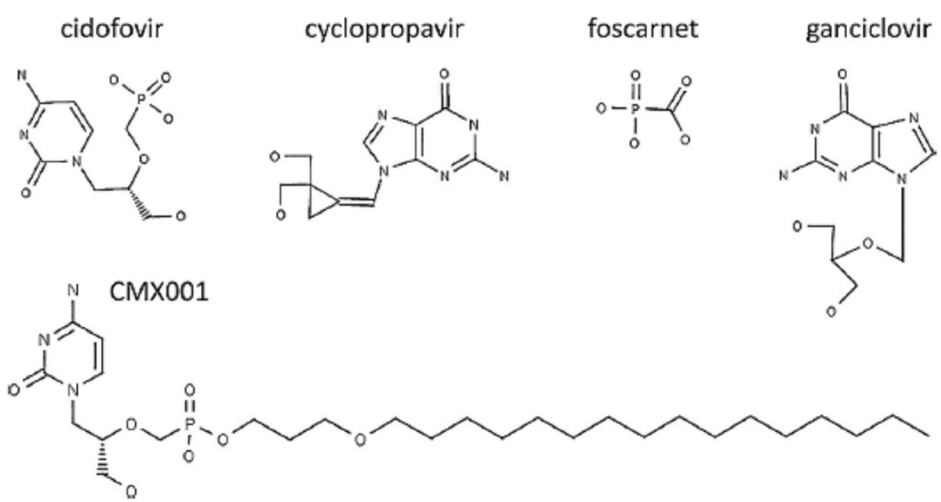


Fig. 2. Selected inhibitors of viral DNA synthesis.

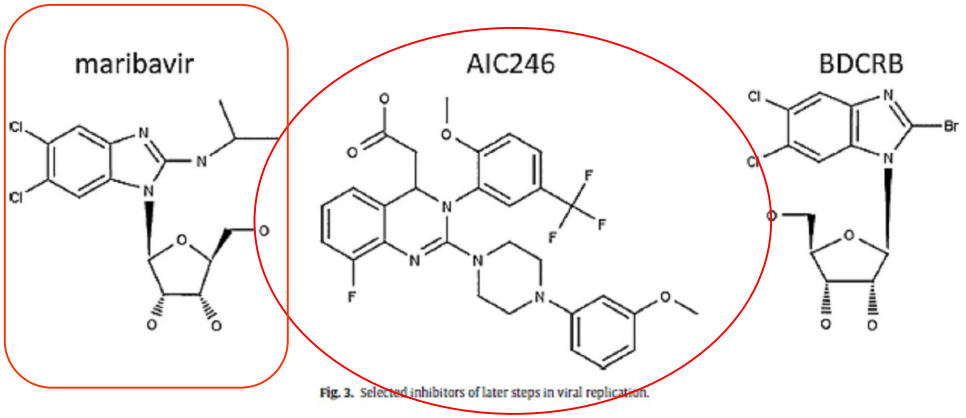
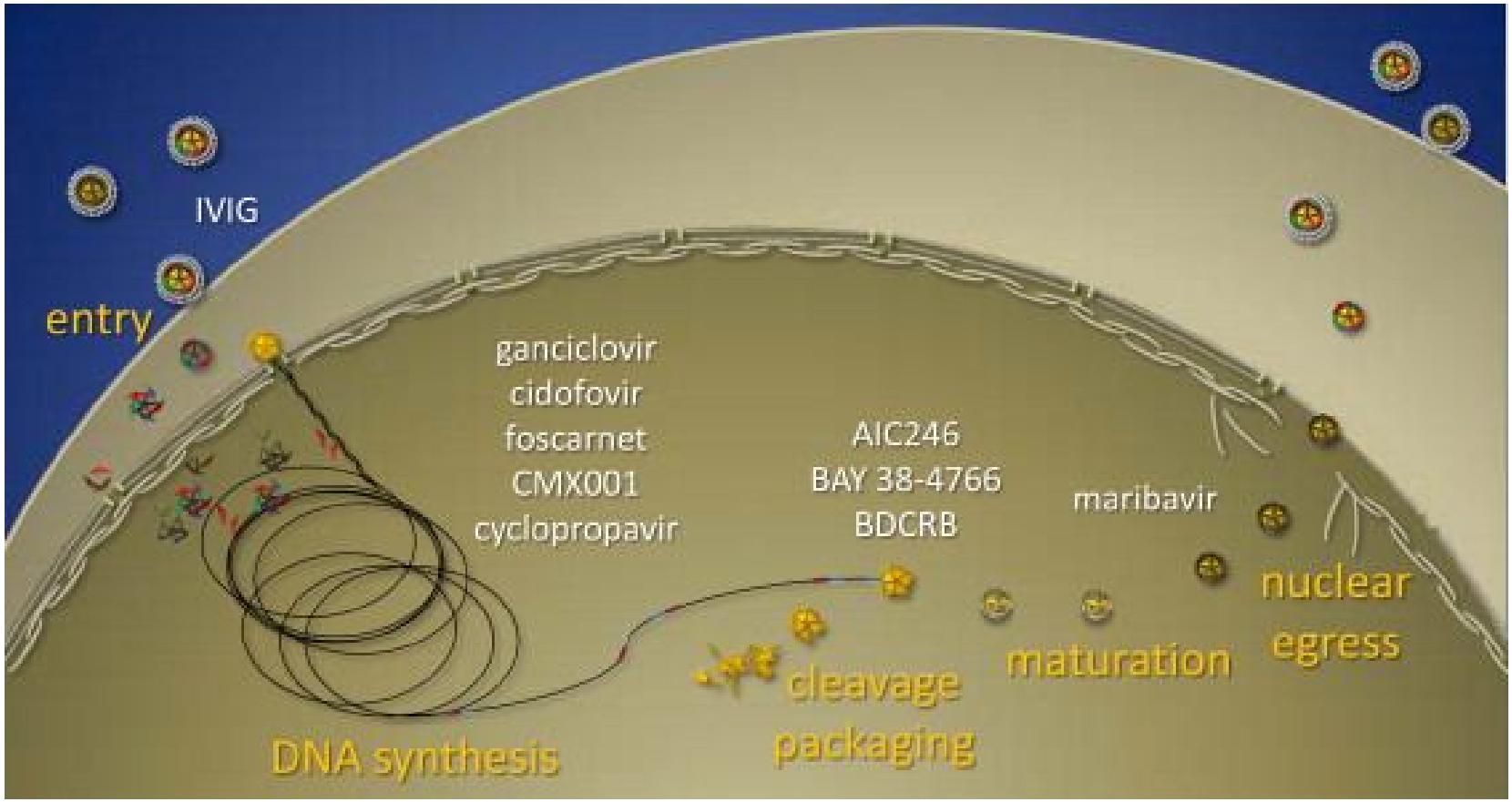


Fig. 3. Selected inhibitors of later steps in viral replication.



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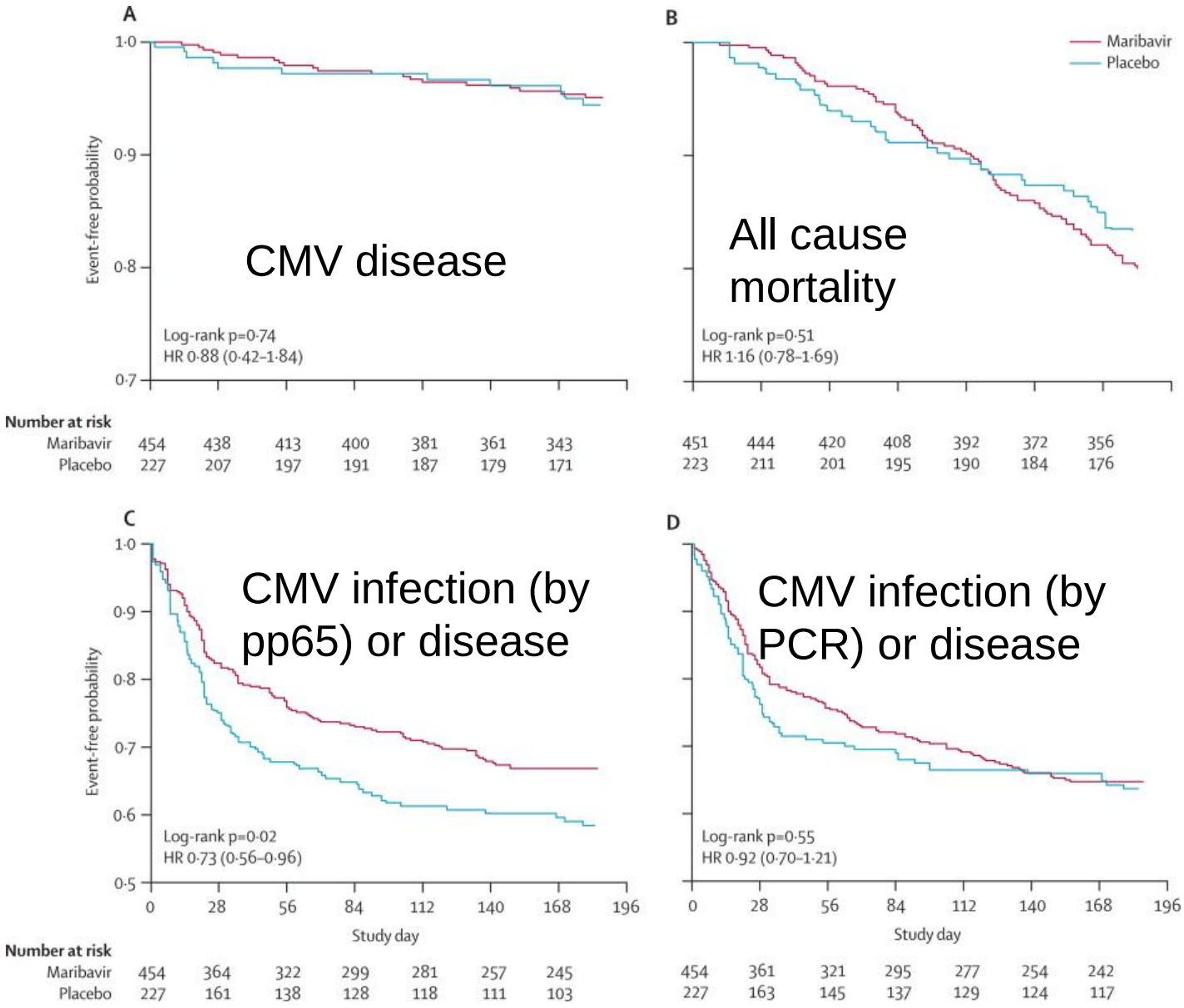
Maribavir prophylaxis in SCT recipient

- Selected good risk patient
- Dose too low
- ?no benefit in viraemia



Marty et al Lancet infect dis April 2011

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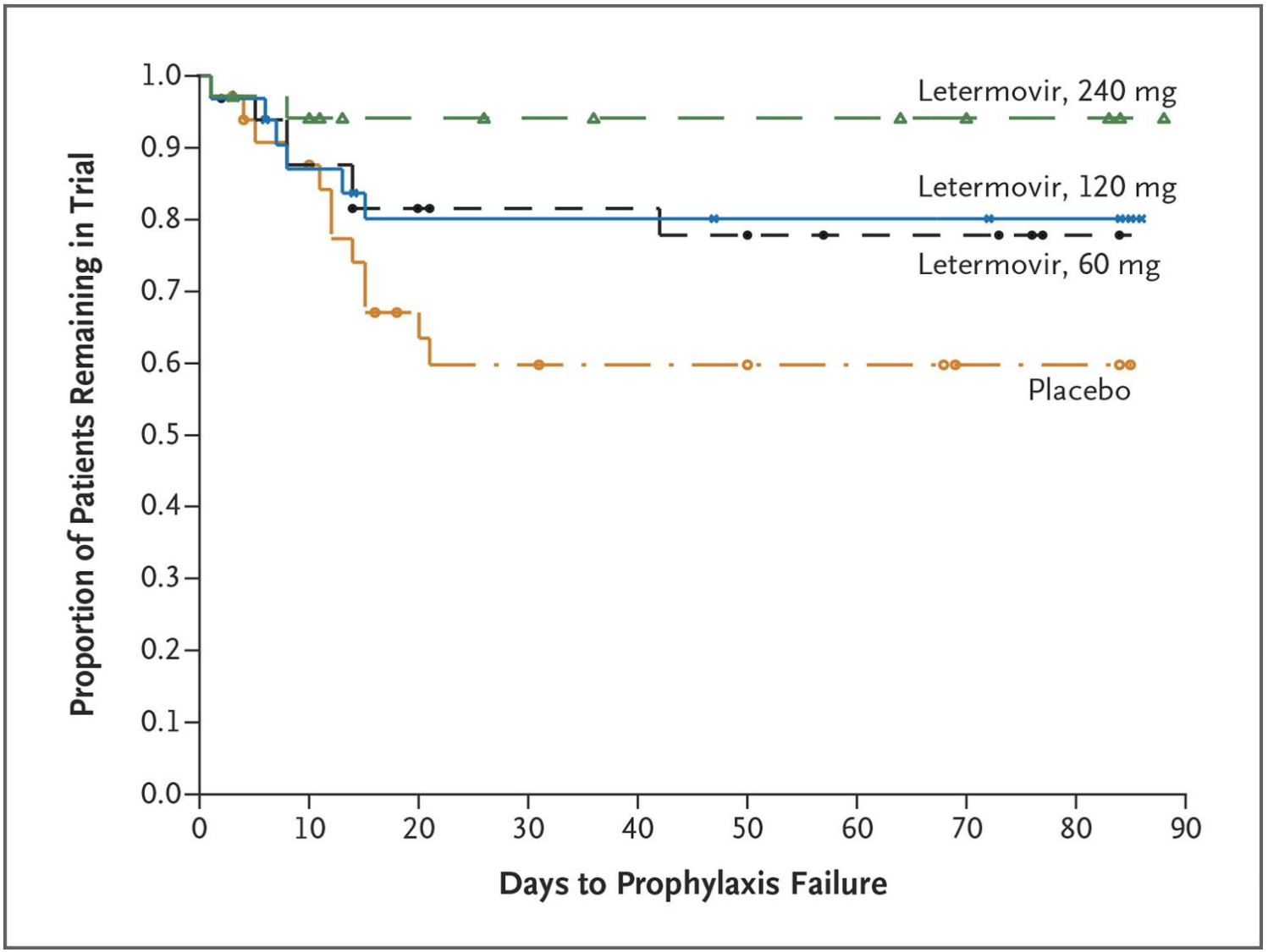
Time to Failure of Prophylaxis against Cytomegalovirus in BMT recipient



Chemaly RF et al. N Engl J Med 2014;370:1781-1789.

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Thank you for your attention